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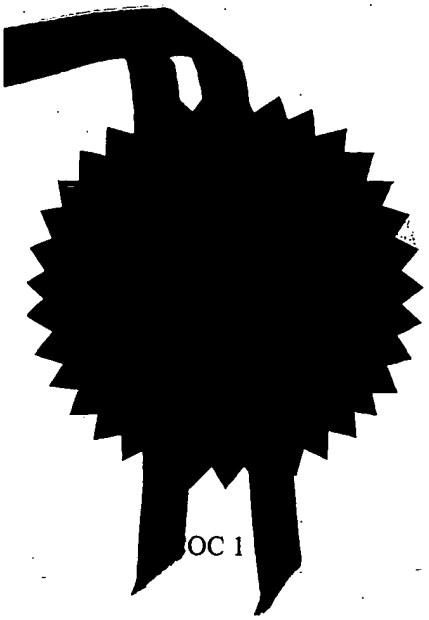

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PATENTS ACT 1977

PATENTS FORM No. 1/77 (Revised 1982)
(Rules 16, 19)

17 DEC 1986

17/12/86 A2939 PAT*** 10.00

The Comptroller
The Patent Office
25 Southampton Buildings
London, WC2A 1AY

1986
30059

REQUEST FOR GRANT OF A PATENT

86 30059

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I Applicant's or Agent's Reference *(Please insert if available)* PLC 428A

II Title of Invention ANTIARRHYTHMIC AGENTS

III Applicant or Applicants *(See note 2)*

Name (First or only applicant) PFIZER LIMITED

Country UNITED KINGDOM State ADP Code No.

Address Ramsgate Road, Sandwich, Kent, CT13 9NJ, England

Name (of second applicant, if more than one)

Country State

Address

IV Inventor (see note 3)

(a) ~~The applicant(s) is/are the sole/joint inventor(s)~~
or
(b) A statement on Patents Form No 7/77 X/will be furnished

V Name of Agent (if any) *(See note 4)* Mr. D. J. Wood ADP CODE NO

VI Address for Service (See note 5)
Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ,

VII Declaration of Priority (See note 6)

Country	Filing date	File number

VIII The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) (See note 7)

Earlier application or patent number ..... and filing date .....

V4919

IX Check List *(To be filled in by applicant or agent)*

A	The application contains the following number of sheet(s)		B	The application as filed is accompanied by:-
1	Request 1	Sheet(s)	1	Priority document ..... ✓
2	Description 13	Sheet(s)	2	Translation of priority document .....
3	Claim(s) ..... ✓	Sheet(s)	3	Request for Search ..... ✓
4	Drawing(s) ..... ✓	Sheet(s)	4	Statement of Inventorship and Right to Grant ..... ✓
5	Abstract ..... ✓	Sheet(s)		

X It is suggested that Figure No ..... ✓ ..... of the drawings (if any) should accompany the abstract when published.

XI Signature *(See note 8)* D. J. Wood

NOTES:

1. This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings.
2. Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg "a corporation organised and existing under the laws of the State of Delaware, United States of America," trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly [known as] ABC Ltd." are not required and should not be given. Also enter applicant(s) ADP Code No. (if known).
3. Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.
4. If the applicant has appointed an agent to act on his behalf, the agent's name and the address of his place of business should be indicated in the spaces available at V and VI. Also insert agent's ADP Code No. (if known) in the box provided.
5. An address for service in the United Kingdom to which all documents may be sent must be stated at VI. It is recommended that a telephone number be provided if an agent is not appointed.
6. The declaration of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.
7. When an application is made by virtue of section 8(3), 12(6), 15(4), or 37(4) the appropriate section should be identified at VIII and the number of the earlier application or any patent granted thereon identified.
8. Attention is directed to rules 90 and 106 of the Patent Rules 1982.
9. Attention of applicants is drawn to the desirability of avoiding publication of inventions relating to any article, material or device intended or adapted for use in war (Official Secrets Acts, 1911 and 1920). In addition after an application for a patent has been filed at the Patent Office the comptroller will consider whether publication or communication of the invention should be prohibited or restricted under section 22 of the Act and will inform the applicant if such prohibition is necessary.
10. Applicants resident in the United Kingdom are also reminded that, under the provisions of section 23 applications may not be filed abroad without written permission or unless an application has been filed not less than six weeks previously in the United Kingdom for a patent for the same invention and no direction prohibiting publication or communication has been given or any such direction has been received.

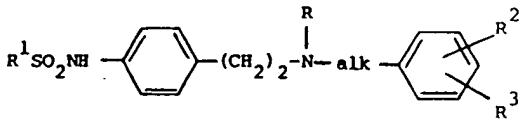
ANTI-ARRHYTHMIC AGENTS

DESCRIPTION

This invention relates to certain sulfonamides which are anti-arrhythmic agents.

The compounds of the invention prolong the duration of the action potential in cardiac muscle and conducting tissue, and thereby increase refractoriness to premature stimuli. Thus, they are Class III antiarrhythmic agents according to the classification of Vaughan Williams (Anti-Arrhythmic Action, E.M. Vaughan Williams, Academic Press, 1980). They are effective in atria, ventricles and conducting tissue both in vitro and in vivo and are therefore useful for the prevention and treatment of a wide variety of ventricular and supraventricular arrhythmias including atrial and ventricular fibrillation. Because they do not alter the speed at which impulses are conducted, they have less propensity than current drugs (mostly Class I) to precipitate or aggravate arrhythmias, and also produce less neurological side effects. Some of the compounds also have some positive inotropic activity and therefore are particularly beneficial in patients with impaired cardiac pump function.

Thus the invention provides compounds of the formula:-



--- (I)

and their pharmaceutically acceptable salts,

wherein R^1 is C_1-C_4 alkyl, C_3-C_7 cycloalkyl, $-CF_3$, $-CH_2Cl$ or $-CH_2CF_3$;

R is C_1-C_4 alkyl;

"alk" is an ethylene, trimethylene or tetramethylene group optionally substituted by a methyl group;

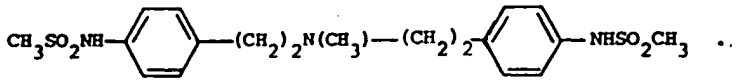
R^2 is H, halo, CF_3 or C_1-C_4 alkyl;

and R^3 is a group of the formula $-NHSO_2R^1$ where R^1 is as

defined above or $-CONR^4R^5$ where R^4 and R^5 are each independently H or C_1-C_4 alkyl or together with the nitrogen atom to which they are attached represent a 1-pyrrolidinyl, piperidino, morpholino or N-methylpiperazin-1-yl group.

"Halo" means F, Cl, Br or I. C_3 and C_4 alkyl groups can be straight or branched chain. "Alk" is preferably $-(CH_2)_n-$ where n is 2, 3 or 4, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)$, $-CH(CH_3)CH_2CH_2-$ or $-CH_2CH_2CH(CH_3)-$.

A preferred individual compound has the formula:-



The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, benzoate, methanesulphonate, besylate and p-toluenesulphonate salts. The compounds also form metal salts, preferred examples of which are the alkaline earth and alkali metal salts. The sodium and potassium salts are most preferred. The salts are preparable by conventional techniques.

For assessment of effects of the compounds on atrial refractoriness, guinea pig right hemiatria are mounted in a bath containing physiological salt solution, and one end is connected to a force transducer. Tissues are stimulated at 1 Hz using field electrodes. Effective refractory period (ERP) is measured by introducing premature stimuli (S_2) after every 8th basic stimulus (S_1). The S_1S_2 coupling interval is gradually increased until S_2 reproducibly elicits a propagated response. This is defined as the ERP. The concentration of compound required to increase ERP by 25% (ED_{25}) is then determined. ERP is also measured in guinea pig right papillary muscles incubated in physiological salt solution. Muscles are stimulated at one end using bipolar electrodes and the propagated electrogram is recorded at the opposite end via a unipolar surface electrode. ERP is determined

as above using the extrastimulus technique. Conduction time is obtained from a digital storage oscilloscope by measuring the interval between the stimulus artefact and the peak of the electrogram (i.e. the time required for the impulse to travel along the length of the muscle).

Atrial and ventricular ERP's are also measured in anaesthetised or conscious dogs by the extrastimulus technique whilst the atrium or right ventricle is being paced at a constant rate.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. They can be administered both to patients suffering from arrhythmias and also prophylactically to those likely to develop arrhythmias. For example they may be administered orally in the form of tablets containing such excipients as starch of lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

For administration to man in the curative or prophylactic treatment of cardiac conditions such as ventricular and supraventricular arrhythmias, including atrial and ventricular fibrillation, it is expected that oral dosages of the compounds of the invention will be in the range from 1 to 75 mg daily, taken in up to 4 divided doses per day, for an average adult patient (70 kg). Dosages for intravenous administration would be expected to be within the range 0.5 to 10mg per single dose as required. A severe cardiac arrythmia is preferably treated by the i.v. route in order to effect a rapid conversion to the normal rhythm. Thus for a typical adult patient individual tablets or capsules might for example contain 1 to 25mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Variations may

occur depending on the weight and condition of the subject being treated as will be known to medical practitioners.

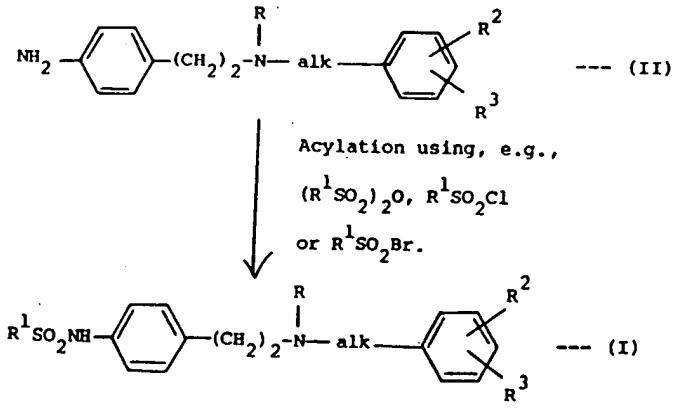
Thus the present invention provides a pharmaceutical composition comprising a compound of the formula (I) as defined above or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a method of preventing or reducing cardiac arrhythmias in a human being, which comprises administering to said human an effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as defined above.

The invention yet further provides a compound of the formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament, particularly as an anti-arrhythmic agent.

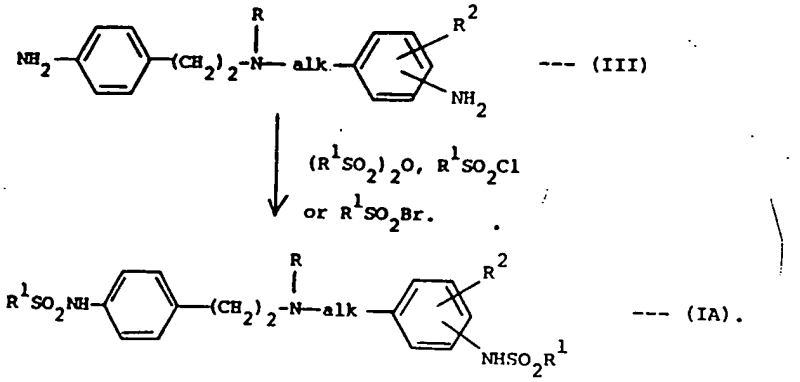
The invention also provides the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or reduction of cardiac arrhythmias.

The compounds of the formula (I) can be prepared by the following general route, in which R, R^1, R^2, R^3 and alk are as defined for formula (I):-



The reaction is typically carried out in a suitable organic solvent, e.g. methylene chloride, at room temperature. It is preferred to use the sulphonic anhydride $(R^1SO_2)_2O$ or sulphonyl chloride R^1SO_2Cl as the sulphonylating agent. The presence of a base such as triethylamine or pyridine is often useful. The product (I) can then be isolated and purified by conventional techniques.

When R^3 is $-NHSO_2R^1$, then the following route is preferred:-

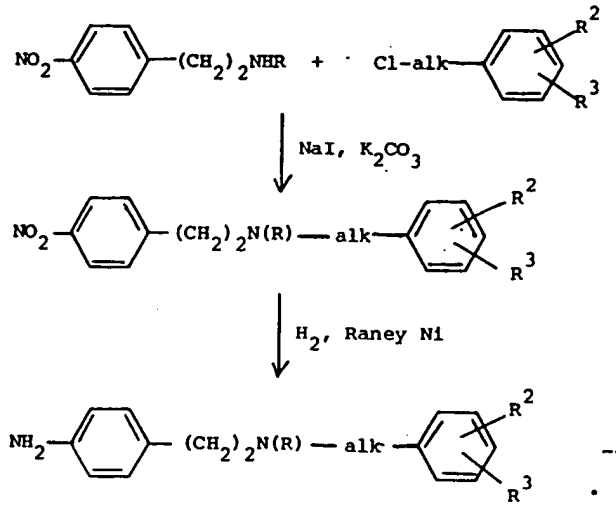


The reaction can again be carried out in a suitable organic solvent, e.g. methylene chloride, at room temperature, although at least 2 equivalents of the sulphonylating agent must of course be used and, in the end product (IA), each R^1 will be the same.

The novel intermediates of the formulae (II) and (III) form a part of the invention.

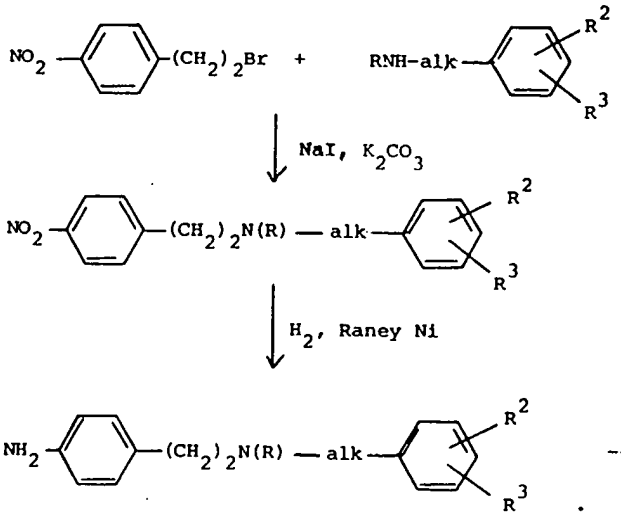
The starting materials for the above routes are obtainable by conventional methods, e.g. as follows:-

(a)


NO2
(CH2)2NHR
+
Cl-alk
R2
R3
NaI, K2CO3
(CH2)2N(R)
alk
H2, Raney Ni
NH2

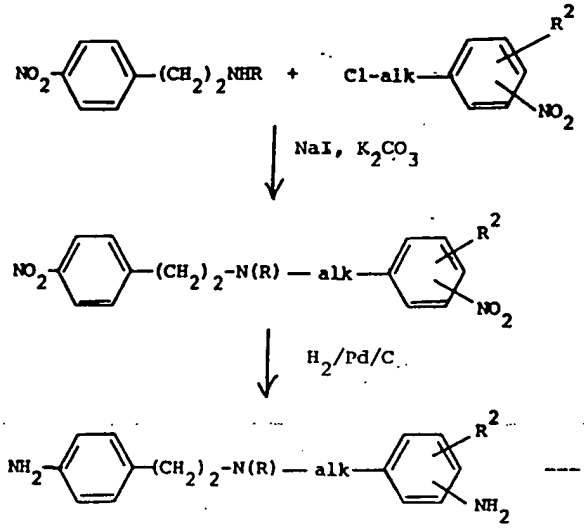
--- (II)

(b)

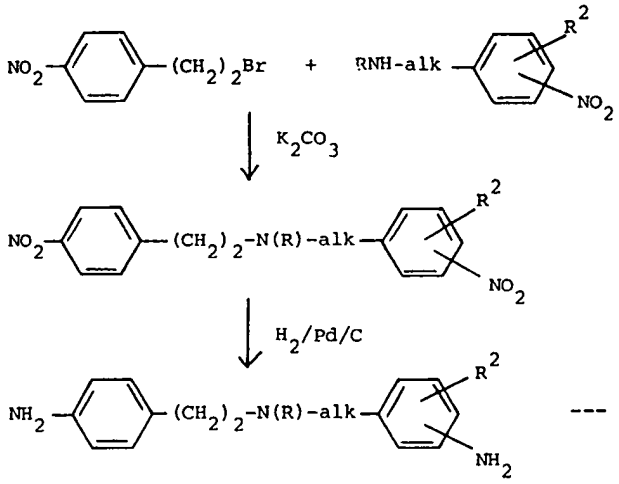

NO2
(CH2)2Br
+
RNH-alk
R2
R3
NaI, K2CO3
(CH2)2N(R)
alk
H2, Raney Ni
NH2

--- (II)

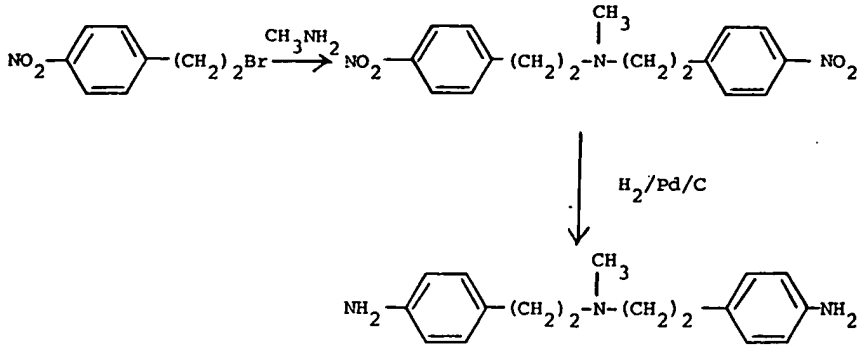
(c)


NO2
(CH2)2NHR
+
Cl-alk
R2
NO2
NaI, K2CO3
(CH2)2-N(R) — alk
H2/Pd/C
NH2
--- (III)

(d)


NO2
(CH2)2Br
+
RNH-alk
R2
NO2
K2CO3
(CH2)2-N(R)-alk
H2/Pd/C
NH2
--- (III)

and (e)



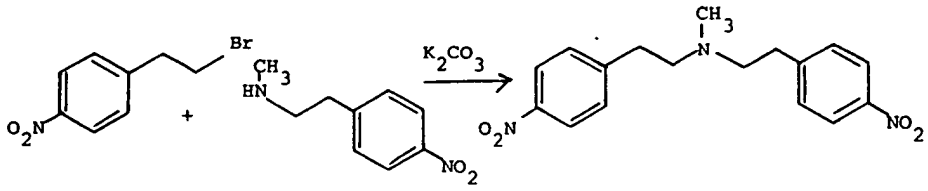
(III)

When the compounds of the formula (I) contain one or more optically active centres, then the invention encompasses both resolved and unresolved forms.

The following Example illustrates the invention. All temperatures are in °C:-

EXAMPLE

(A) N,N-Bis-(4-nitrophenethyl)methylamine



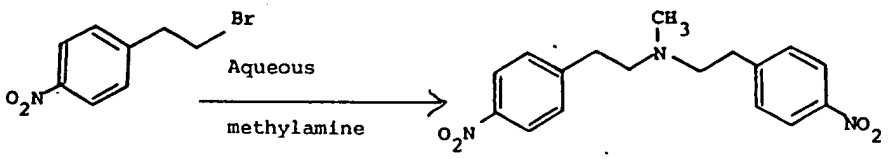
The title compound is a known compound having been isolated as a by-product (7%) from the reaction of 4-nitrostyrene and methylamine. [See Journal Organic Chemistry 1956 Vol. 21 p. 45.] However, it is preferred to make this compound by the route described below.

4-Nitrophenethyl bromide (2.6 g, 11.3 mmol), N-methyl-4-nitrophenethylamine (2.0 g, 11.3 mmol) and potassium carbonate (1.6 g, 11.3 mmol) in acetonitrile were stirred at the reflux temperature for 4 days. The solvent was then removed and the residue was taken up in ethyl acetate, washed three times with aqueous sodium carbonate and three times with brine, dried ($MgSO_4$) and evaporated. The resultant oil was chromatographed on silica eluting with methylene chloride containing methanol (0% up to 2%). The appropriate fractions were combined and evaporated to give an orange oil which was triturated with hexane to give an orange powder which was filtered and dried, yield of the title compound, 1.3 g, m.p. 70-71°.

Analysis %:-

Found:	C,61.7; H,5.75; N,12.5;
Calculated for $C_{17}H_{19}N_3O_4$:	C,62.0; H,5.8; N,12.8.

Alternative preparation of N,N-bis-(4-nitrophenethyl)methylamine

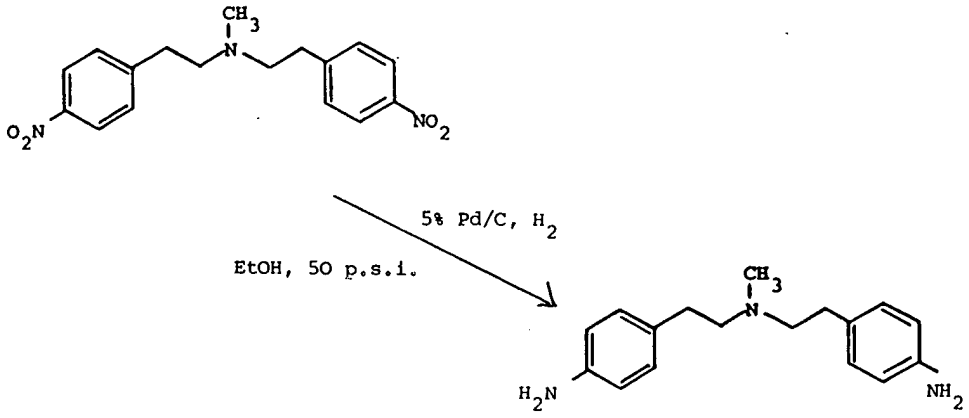


4-Nitrophenethyl bromide (1.0 g, 4.35 mmol) and 33% methylamine in water (10 ml) were stirred together at 55° for 2 hours. The reaction mixture was cooled and the resulting precipitate was collected by filtration and purified by column chromatography on silica eluting with methylene chloride containing methanol (0% up to 5%). The appropriate fractions were combined and evaporated to give the title compound, yield 0.19 g, m.p. 73-75°.

Analysis %:-

Found:	C,62.2; H,5.9; N,12.6.
Calculated for $C_{17}H_{19}N_3O_4$:	C,62.0; H,5.8; N,12.8.

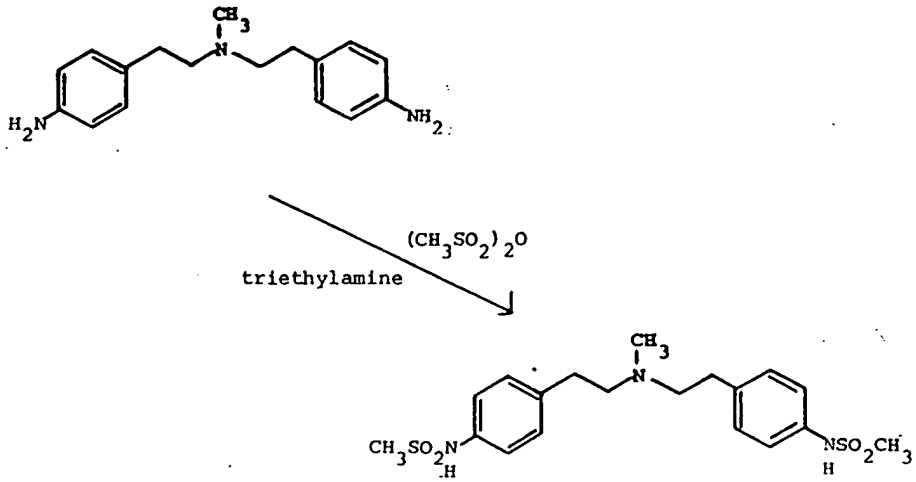
(B) N,N-Bis(4-aminophenethyl)methylamine



A solution of N,N-bis-(4-nitrophenethyl)methylamine (1.2 g, 3.6 mmol) in ethanol (50 ml) containing 5% Pd/C (0.15 g) was stirred under a hydrogen atmosphere (50 p.s.i.) for 4 hours. The reaction mixture was filtered and the solvent evaporated to give the title compound as an oil, yield 1.0 g, which was used directly without further purification.

N.M.R. ($CDCl_3$), δ = 6.7 (q, 8H); 3.4 (br s, 4H); 2.6 (s, 8H); 2.3 (s, 3H).

(C) N,N-Bis-(4-methanesulphonamidophenethyl)methylamine



Methanesulphonic anhydride (1.29 g, 7.4 mmole) was added to a solution of N,N-bis-(4-aminophenethyl)methylamine (1.0 g, 3.7 mmole) and triethylamine (1 ml, 7.4 mmole) in dry methylene chloride (50 ml) and stirred at room temperature for 2 hours. Methanesulphonic anhydride (1.29 g, 7.4 mmole) was added and the reaction mixture was stirred for a further 2 hours. The solvent was removed and the residue was taken up in methylene chloride,

washed three times with aqueous sodium bicarbonate and three times with brine, dried ($MgSO_4$), and evaporated. The resultant oil was chromatographed on silica eluting with methylene chloride containing methanol (0% up to 5%), which after combination and evaporation of the appropriate fractions, gave the title compound, yield 0.29 g, m.p. 170-171°.

Analysis %/:-

Found:	C,53.15; N,6.5; H,9.7;
Calculated for $C_{19}H_{27}N_3O_4S_2$:	C,53.6; N,6.4; H,9.8*.

N.M.R. (TFAD), δ = 7.1 (q, 8H); 3.5 (m, 4H); 3.3 (m, 4H); 3.0 (s, 6H); 2.95 (s, 3H).

*The sample contained a trace of methylene chloride (1/20 mole CH_2Cl_2 as adjudged by ^{1}H-n.m.r. spectroscopy).

It will be appreciated from the foregoing that what we will claim may include the following:

(1) The compounds of the formula (I) and their pharmaceutically acceptable salts;

(2) Processes as described herein for preparing the compounds of the formula (I) and their slats;

(3) Pharmaceutical compositions comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier;

(4) A compound of the formula (I) for use as a medicament;

(5) The use of a compound of the formula (I), or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or reduction of cardiac arrhythmias; and

(6) Any novel intermediates described herein.